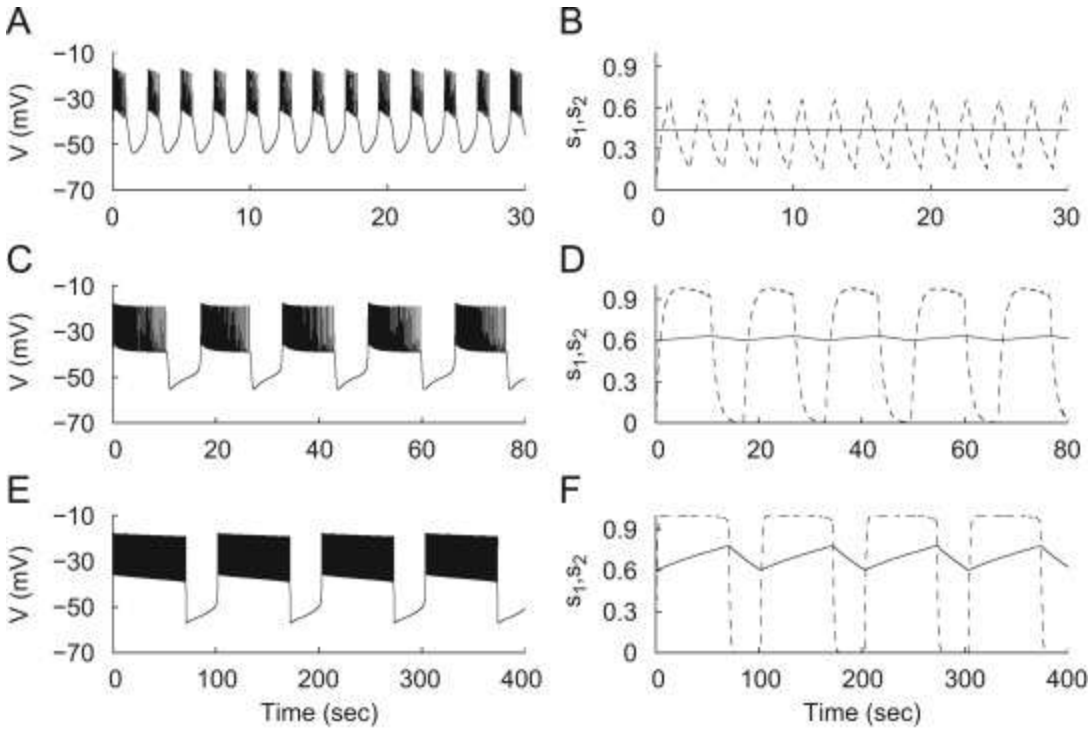
Dynamics in Neural, Endocrine and Metabolic Systems
A Symposium in Honor of Arthur Sherman

Over 28 years of scientific contribution to the field of mathematical biology



Thursday, June 7

Mark Reitman (Chief of the Diabetes, Endocrinology, and Obesity Branch, National Institutes of Health) 8:30-8:45
Opening Remarks

John Rinzel (New York University) 8:45-9:00
Overview of the History of MRB/LBM and Dr. Sherman's Contribution to it

Richard Bertram (Florida State University) 9:00-9:25
The Dual Oscillator Model for Islet Oscillations
Abstract: Since the publication of the first mathematical model of the pancreatic islet much progress has made in understanding the biophysical mechanisms underlying the islet's bursting electrical activity. This activity underlies pulsatile insulin secretion, which is a hallmark of normal glucose homeostasis. In this presentation I discuss a model that combines electrical, calcium, and metabolic components to produce the types of oscillations observed in mouse islets under a range of conditions. The model was developed over many years of research in collaboration with Artie Sherman, Les Satin, and numerous students, postdocs, and research scientists.

Paula B. Goforth (University of Michigan) 9:30-9:55
Experimental Tests of the Islet Dual Oscillator Model
Abstract: The Dual Oscillator Model (DOM) is the latest in a series of dynamical models of islet function. The model consists of equations describing ion channel excitability, intracellular free Ca^{2+} handling, mitochondrial function and slow feedback mediated by the glycolytic enzyme phosphofructokinase-M. Experimental tests of the DOM included 'stress testing' mouse islet responses to glucose and demonstrating the nature of the interaction between metabolism and $[Ca^{2+}]_i$. Most recently we have been testing how the generation and metabolism of the glycolytic metabolite fructose 2,6 bisphosphate in beta cells affects the DOM. We are also testing whether the DOM successfully predicts the slow dynamics of K_{ATP} conductance changes during bursting. Supported by RO1 DK46409 (to L. S.).

Morten Gram Pedersen (University of Padova) 10:00-10:25
From Mice to Men: Modeling Electrical Activity in Human Beta-Cells
Abstract: Electrical activity in pancreatic beta-cells plays a pivotal role in glucose-stimulated insulin secretion by coupling metabolism to calcium-triggered exocytosis. Mathematical models based on rodent data have helped in understanding the mechanisms underlying the electrophysiological patterns observed in laboratory animals. However, human beta-cells differ in several aspects, and in particular in their electrophysiological characteristics, from rodent beta-cells. Hence, from a clinical perspective and to obtain insight into the defects in insulin secretion relevant for diabetes mellitus, it is important to study human beta-cells. We use a recently developed mathematical model of electrical activity based entirely on detailed ion channel characteristics of human beta-cells, to investigate various patterns of electrical activity, and interpret atypical and non-intuitive responses to ion channel blockers in human beta-cells. I will also present a mathematical analysis of how rapid bursting occurs in the model using the theory of mixed-mode oscillations, singular Hopf bifurcations and canards.

Coffee Break 10:30-10:45

Charles S. Peskin (Courant Institute of Mathematical Sciences) 10:45-11:10
On the Unification of Cardiac Mechanics and Electrophysiology by the Immersed Boundary Method
Abstract: The immersed boundary method was introduced for studying flow patterns around heart valves, and has since been applied to computer modeling of fluid-structure interaction in the heart as a whole. Unexpectedly, there is a formal analogy between the equations of cardiac mechanics and the bidomain equations of cardiac electrophysiology, and this leads to a generalization of the immersed boundary method that can be used to formulate and solve the dynamical equations of a combined electrical, mechanical, and fluid-mechanical model of the heart.

Lisa Fauci (Tulane University) 11:15-11:40
A Tale of Waving Tails: Calcium-Driven Dynamics of Undulatory Swimmers
Abstract: Locomotion due to body undulations is observed across the entire spectrum of swimming organisms, from microorganisms to fish. The internal force generating mechanisms range from the action of dynein molecular motors within a mammalian sperm to muscle activation in lamprey. We will present recent progress in building multiscale computational models that couple biochemistry, passive elastic properties and active force generation with a surrounding fluid for these two swimmers.

Gerda de Vries (University of Alberta) 11:45-12:10
Quantitative Analysis of Single Particle Tracking Experiments: Applying Ecological Methods in Cell Biology
Abstract: A commonly used experimental technique to study the movement of biomolecules in the cell membrane is Single Particle Tracking (SPT). SPT involves tagging biomolecules with a fluorescent label and observing and recording their trajectories over time. A diffusion coefficient then can be extracted from the data from mean square displacement calculations. Although the diffusion coefficient provides an overall measure of mobility, it does not provide insight into the underlying heterogeneity of the membrane environment.

Since the method of data collection from individual biomolecules is analogous to that from individual animals, we propose to use methods from ecology to provide spatial insight. Ecologists regularly quantify animal movement using the concepts of correlated random walk, net squared displacement, and first-passage time. In this talk, we will demonstrate the applicability of

these methods in the context of cell biology. In particular, we will show how we can distinguish biomolecule trajectories undergoing a correlated random walk from those that do not, and how we can identify the presence of transient confinement zones in molecular diffusion.

Lunch 12:15-1:40

John Rinzel (New York University) 1:40-2:05
Slope-Based Stochastic Resonance
Abstract: Many neurons fire repetitively in response to steady input. Phasic neurons, however, fire only at the onset of a steady input. For time-varying inputs, phasic neurons are band-pass filters or slope detectors. We have shown that noise enables a phasic model to encode transient features of slow inputs with slopes that are below their deterministic threshold levels. This stochastic-resonance (SR) like effect differs significantly from the classical SR behavior. Instead of being most sensitive to the peak of a subthreshold signal, as is typical in a classical SR system, phasic models are most sensitive to the signal's rising and falling phases.

David Terman (Ohio State University) 2:10-2:35
Modeling the Neuroprotective Role of Stimulating Glial Mitochondria During Stroke
Abstract: We present a mathematical model that integrates the dynamics of cell membrane potential, cell volume, mitochondrial and ER calcium handling and $P2Y_1$ receptor stimulation. Simulations of the model support recent experimental data showing the protective effect of stimulating astrocytic $P2Y_1$ receptors following ischemia. An important goal of the paper is to mathematically analyze the model in order to better understand mechanisms underlying the experimental results and model behavior. The mathematical analysis leads to explicit formulas that determine how changes in IP_3-mediated Ca^{2+} release and the pyruvate and external oxygen levels effect mitochondrial ATP production. This is joint work with Casey Diekman, Chris Fall and Jim Lechleiter.

Elise Stanley (University of Toronto) 2:40-3:05
On Caclium Channels, Synapses and Sandwiches
Abstract: The cell bodies of dorsal root ganglia neurons are mostly isolated from each other by individual sheathes of satellite glial cells. However, a significant fraction are in close contact, separated only by a narrow, single glial membrane sheet. Double voltage clamp recordings showed that stimulation of one neuron soma with a train of impulse-like depolarizations reliably triggered a slow response in the partner soma. Transmission was found to be transglial with two synapses in series. We term this novel mechanism of inter-neuron communication, which may be common in the nervous system, a 'Sandwich Synapse'.

Coffee Break 3:10-3:25

Gregory D. Smith (College of William & Mary) 3:25-3:50
Modeling the Bidirectional Coupling of Localized Calcium Elevations and Whole Cell Calcium Responses
Abstract: Localized Ca elevations known as Ca puffs and sparks are cellular signals that arise from the cooperative activity of clusters of inositol 1,4,5-trisphosphate receptors and ryanodine receptors clustered at Ca release sites on the surface of the endoplasmic reticulum or sarcoplasmic reticulum. When Markov chain models of intracellular Ca regulated Ca channels are coupled via a mathematical representation of a Ca microdomain, simulated Ca release sites may exhibit the phenomenon of stochastic Ca excitability where the IP3Rs or RyRs open and close in a concerted fashion. Such mathematical models provide insight into the relationship between single-channel kinetics and the statistics of puff/spark duration, and clarify the role of stochastic attrition, Ca inactivation, luminal depletion, and allosteric interactions in the dynamics of puff/spark termination. The stochastic dynamics of local Ca is an important aspect of excitation-contraction coupling in cardiac myocytes, where sarcoplasmic reticulum Ca-induced Ca release is locally controlled by trigger Ca influx via L-type channels of the plasma membrane. A recently developed whole cell modeling approach is able to avoid the computationally demanding task of resolving spatial aspects of global Ca signaling by using probability densities and associated moment equations to representing heterogeneous local Ca signals in a population of Ca release units. This new class of whole cell models of Ca handling facilitates simulation and analysis of the bidirectional coupling of localized calcium elevations and whole cell calcium responses in cardiac myocytes.

Sue Moenter (University of Michigan) 3:55-4:20
The Ups and Downs of Gonadotropin-Releasing Hormone (GnRH) Neurons
Abstract: GnRH neurons form the final common pathway for the central regulation of reproduction. Their output is episodic (pulsatile) and frequency modulated; both features are critical to normal reproductive cycles in females. Recently, a *biological* model was proposed in which GnRH pulse generation was outsourced to a neuronal population in the arcuate nucleus of the hypothalamus. These KNDy neurons coexpress kisspeptin, neurokinin B and dynorphin and are proposed to act as a self-stimulating (NKB) and self-inhibiting (dynorphin) network that sends excitatory information to GnRH neurons via the neuromodulator kisspeptin to initiate pulsatile release. Data will be presented from electrophysiological studies designed to test aspects of this biological model, and also feedback interactions from GnRH neurons to this population. The data were collected by Zhiguo Chu and Kristen Ruka.

Yue-Xian Li (University of British Columbia) 4:25-4:50
How a Diffusive Autocrine Signal Synchronizes Nonlinear Oscillators that are Diffusely Distributed in Space?
Abstract: This talk discusses how diffusely distributed nonlinear oscillators (i.e. cells or neurons) in space can be synchronized by a diffusive autocrine signal. The signal is "autocrine" since it is secreted/released by each cell and at the same time acts on each cell to exert important influences on the release of the signal. We aim at developing a theory that outline conditions under which synchronized oscillations occur in such a system. The problem becomes more interesting in case each cell, when isolated, is a

conditional oscillator (i.e. a system with a potential of generating oscillations but remain quiescent at a stable steady state near a threshold of transition to oscillations). Such a theory has numerous applications ranging from the synchronization of GnRH neurons in the hypothalamus to other systems of spatially distributed cell cultures such as cultures of embryonic cardiac cells. The theory can also be applied to some cases of quorum sensing, a widely observed phenomenon in multi-cellular systems.

Group Photo 5:00

Dinner Banquet 6:30

Friday, June 8

Krasimira Tsaneva-Atanasova (University of Bristol) 9:00-9:25
Modeling and Analysis of Pseudo-Plateau Bursters
Abstract: In this talk I will present and discuss mathematical models of pseudo-plateau bursting. Specifically I will focus on pituitary somatotrophs and inner hair cells. Pituitary somatotrophs release growth hormone in response to spontaneous calcium entry through voltage-gated calcium channels, which is governed by plateau-bursting electrical activity and is regulated by several neurohormones. Inner Hair Cells are the first receptor cells of hearing and are connected to the afferent nerves. Sound transduction by inner hair cells is mediated via secretion of neurotransmitters. The patterns of secretion are governed by electrical activity, whose amplitude and phase drive auditory nerve firing. Although functionally different these two cellular systems are remarkably similar in regard to the mechanisms that underlie their electrical activity. In both cases our models were validated against experimentally-observed patterns of activity, such as spiking and pseudo-plateau bursting. The involvement of intracellular calcium stores in regulating the intracellular calcium signal, important for local dynamic fine-tuning of the membrane potential dynamics, is studied based on model results.

Hinke Osinga (University of Aukland) 9:30-9:55
The Codimension of Pseudo-Plateau Bursting
Abstract: A great deal of work has gone into classifying bursting oscillations, periodic alternations of spiking and quiescence modeled by fast-slow systems. In such systems, one or more slow variables carry the fast variables through a sequence of bifurcations that mediate transitions between oscillations and steady states. A rigorous classification approach is to characterize the bifurcations found in the neighborhood of a singularity; a measure of the complexity of the bursting oscillation is then given by the smallest codimension of the singularities near which it occurs. Fold/homoclinic bursting, along with most other burst types of interest, has been shown to occur near a singularity of codimension three by examining bifurcations of a cubic Lienard system; hence, these types of bursting have at most codimension three. Modeling and biological considerations suggest that fold/homoclinic bursting should be found near fold/subHopf bursting, a more recently identified burst type whose codimension has not been determined yet. One would expect that fold/subHopf bursting has the same codimension as fold/homoclinic bursting, because models of these two burst types have very similar underlying bifurcation diagrams. However, no codimension-three singularity is known that supports fold/subHopf bursting, which indicates that it may have codimension four. We identify a three-dimensional slice in a partial unfolding of a doubly-degenerate Bodganov-Takens point, and show that this codimension-four singularity gives rise to almost all known types of bursting.

Bernd Krauskopf (University of Auckland) 10:00-10:25
Finding Slow Manifolds that Organize Mixed-Mode Oscillations
Abstract: We present a general numerical method to compute attracting and repelling slow manifolds and associated canard orbits in systems with a splitting of time scales. As is demonstrated with the self-coupled FitzHugh-Nagumo system, these mathematical objects are of interest as global organizors of mixed-mode oscillations. This is joint work with Matheiu Desroches (INRIA) and Hinke Osinga (The University of Auckland).

Coffee Break 10:30-10:45

Bard Ermentrout (University of Pittsburgh) 10:45-11:10
Weak and Slow: Spatial Patterns in a Heterogeneous Environment
Abstract: I look at the interactions between heterogeneities and delayed negative feedback in systems which admit stationary persistent structures. The former can cause pinning and stabilize neutrally stable dynamics while the latter can induce several types of dynamics instabilities and motion. I show that the time-scale of the negative feedback and the amplitude of the heterogeneities interact to produce qualitatively different sequences of bifurcations. The models are motivated by dynamics of neurons in the rodent hippocampus during navigation. This work is joint with Rodica Curtu, Carina Curto, and Vladimir Itskov.

Stanko S. Stojilkovic (National Institutes of Health) 11:15:11:40
Gating Properties of Purinergic P2X Receptor Channels
Abstract: Mammalian adenosine-5'-triphosphate (ATP)-gated non-selective cation channels (P2XRs) can be composed of seven possible subunits, denoted P2X1 to P2X7. Each subunit contains a large ectodomain, two transmembrane domains and intracellular N- and C-termini. Functional P2XRs are organized as homomeric and heteromeric trimers. The ectodomains contain three ATP binding sites, presumably located between neighboring subunits and formed by highly conserved residues. The gating of P2XRs usually consists of three phases: a rapid rising phase of inward current induced by the application of agonist (activation phase), a slowly developing decay phase in the presence of an agonist (desensitization phase), and a relatively rapid decay of current after

ATP is removed (deactivation phase). On the other hand, the profile of P2X7R current is more complex, as indicated by the secondary current growth during sustained agonist application. The slow secondary growth of current in the biphasic P2X7R response coincides temporally with pore dilation. The current knowledge on receptor-specific gating properties will be presented. A work in progress on the relationship between the pattern of gating and receptor function will also be discussed.

Anmar Khadra (McGill University) 11:45-12:10

Markov State Models for P2X Receptor-Channels: Bistability and Beyond

Abstract: Purinergic P2X receptors are a family of ATP-gated ion channels composed of seven subunits labelled P2X1-7. They are expressed in excitable and non-excitable cells, such as neurons and lymphocytes, and are involved in many biological processes (e.g., synaptic transmission, hormone secretion, inflammation and chronic pain). They possess three binding sites that, when occupied by ATP, lead to receptor activation and channel opening. We have developed Markov state kinetic models of two members of this family of receptors. Our goal was to explore possible mechanisms underlying the kinetic behavior and gating properties of these receptors upon ATP stimulation. More specifically, we investigated why these receptors exhibit two opposite activation-dependent changes, pore dilation and pore closing. A brief overview of these results will be presented in this talk.

Lunch 12:15-1:30

Samuel W. Cushman (National Institutes of Health) 1:30-1:55

Regulation of Adipose Cell Growth and Turnover, and Its Dysfunction in Insulin Resistance

Abstract: The biological mechanism by which obesity predisposes to insulin resistance is unclear. While adipose cell size is known to increase in proportion to BMI, it has not been clearly shown that cell size, independent of BMI, is associated with insulin resistance. Here we report the results of several studies aimed at reexamining this relationship.

Initially, we compared adipose cell size distribution in 28 equally obese, otherwise healthy individuals who represented extreme ends of the spectrum of insulin sensitivity, as defined by the modified insulin suppression test. All individuals exhibited a non-unimodal cell size distribution featuring an approximately normal peak of large cells and a tail of small cells. Contrary to expectations, the mean diameter of the larger cells was not significantly different between the insulin-sensitive and insulin-resistant individuals, but rather insulin resistance was associated with a higher ratio of small to large cells. Similar cell size distributions were observed for isolated adipose cells. Further, real-time PCR results showed two- to threefold lower expression of genes encoding markers of adipose cell differentiation in insulin-resistant compared with insulin-sensitive individuals. These results demonstrate that after controlling for obesity, insulin resistance is associated with an expanded population of small adipose cells and decreased expression of differentiation markers, suggesting that impairment in adipose cell differentiation may contribute to obesity-associated insulin resistance.

We then sought to determine whether increased adipose cell size is associated with localized inflammation in weight-stable, moderately obese humans. We recruited 49 healthy, moderately obese individuals for quantification of insulin resistance (modified insulin suppression test) and subcutaneous abdominal adipose tissue biopsy. Adipose cells were again non-unimodally distributed, with 47% in a 'large' cell population and the remainder in a 'small' cell population. The median diameter of the large adipose cells was not associated with expression of inflammatory genes. Rather, the fraction of small adipose cells was consistently associated with inflammatory gene expression, independently of sex, insulin resistance and BMI. This association was more pronounced in insulin-resistant than insulin-sensitive individuals. Insulin resistance also independently predicted expression of inflammatory genes. This study demonstrates that among moderately obese, weight-stable individuals an increased proportion of small adipose cells is associated with inflammation in subcutaneous adipose tissue, whereas size of mature adipose cells is not. The observed association between small adipose cells and inflammation may reflect impaired adipogenesis and/or terminal differentiation.

Another study was initiated to compare the characteristics of adipose cells in subcutaneous and omental visceral adipose tissue (SAT and VAT, respectively); in this instance, individuals were chosen to be insulin-resistant, but varied in degree of adiposity. We compared adipose cell size distribution and genetic markers, in SAT and VAT of individuals undergoing bariatric surgery. While the proportion of small cells and expression of adipocyte differentiation genes did not differ between depots, inflammatory genes were upregulated in VAT. The diameter of SAT large cells correlated highly with increasing proportion of small cells in both SAT and VAT. No associations were observed between VAT large cells and cell size variables in either depot. The effect of body mass index (BMI) on any variables in both depots was negligible. Thus, the major differential property of VAT in IR women is increased inflammatory activity, independent of BMI. The association of SAT adipocyte hypertrophy with hyperplasia in both depots suggests a primary role SAT may have in regulating regional fat storage.

Finally, we carried out a study in human subjects to determine whether pioglitazone stimulates adipogenesis *in vivo* and whether this process relates to improved insulin sensitivity. To test this hypothesis, 12 overweight/obese nondiabetic, insulin-resistant individuals underwent biopsy of abdominal subcutaneous adipose tissue at baseline and after 12 weeks of pioglitazone treatment. Insulin resistance (steady-state plasma insulin and glucose (SSPG)) decreased following pioglitazone treatment. There was an increase in the ratio of small-to-large adipose cells, as well as a 25% increase in the absolute number of small adipose cells. The distribution of large cell diameters widened, but the diameter did not increase in the case of the small cells. The increase in the proportion of small cells was associated with the degree to which insulin resistance improved. Visceral abdominal fat decreased, and subcutaneous abdominal and femoral fat increased significantly. Changes in fat volume were not associated with SSPG change. These findings demonstrate a clear effect of pioglitazone on human subcutaneous adipose cells, suggestive of adipogenesis in abdominal subcutaneous adipose tissue, as well as redistribution of fat from visceral to subcutaneous depots, highlighting a potential mechanism of action for thiazolidinediones. These findings support the hypothesis that defects in subcutaneous fat storage may underlie obesity-associated insulin resistance.

Kevin D. Hall (National Institutes of Health) 2:00-2:25

The Calculus of Calories: Mathematical Modeling of Body Weight Dynamics

Abstract: I will describe how mathematical models can be used to investigate human metabolism and provide a quantitative framework for integration of metabolic and body composition data. Several such models have recently been developed by my group to make quantitative predictions about how diet perturbations result in adaptations of energy expenditure and metabolic fuel selection. I will show that our models accurately predict body weight and composition changes during controlled feeding experiments and help us understand the underlying dynamics of energy imbalance. The models can be used to help design and interpret clinical research studies, help set individual weight loss goals and track adherence to lifestyle interventions, and evaluate potential effects of population level interventions targeted to address the obesity epidemic.

Carson Chow (National Institutes of Health) 2:30-2:55

The Shape of Obesity

Abstract: The mean body weight in the US increased by about 20 pounds between 1975 and 2005. However, the weight increase was not uniform across the population. The body mass index distribution has also become wider over that time. A third of the population is now obese, but a third seems to be immune to the obesity epidemic. Recent metabolic modeling has shown that the more body fat a person has the more weight they will gain for the same increase in caloric intake. Hence, it is possible that the spread in the distribution is caused by a uniform increase in food intake. I will address this question using Bayesian model comparison methods.

Coffee Break 3:00-3:15

Vipul Periwal (National Institutes of Health) 3:15-3:40

The Architecture of the Islets of Langerhans

Abstract: What determines the range of islet sizes observed in nature and the distribution of beta and alpha cells within each islet? Results on the dynamics of the islet size distribution in development, obtained using novel large-scale imaging data obtained by the Hara laboratory, will be presented. The study of islet architecture has led us to hypothesize that islet morphology differences between species may be due to species-specific endocrine cell fractions, rather than species-specific cell-cell adhesion properties. We have carried out model simulations that support our hypothesis, and an ongoing collaboration with the Foty laboratory has provided in vitro experimental support.

Victor Matveev (New Jersey Institute of Technology) 3:45-4:10

Non-local Amplification of Ca2+ Signals by Ca2+ Buffer Saturation: A Computational Study

Abstract: Endogenous calcium (Ca2+) buffers are abundant in all cell types, and play an important part in cell Ca2+ homeostasis. Although the role of many Ca2+ buffering molecules is known to go beyond direct regulation of free Ca2+ concentration, even "passive" Ca2+ buffering can lead to non-trivial dynamical effects on Ca2+ dependent processes. In particular, saturation of high-affinity buffers has been proposed as a potential mechanism of short-term facilitation of synaptic response (Neher, 1998), and has been confirmed to contribute to facilitation at calbindin-positive mammalian central synapses (Blatow et al, 2003). In the buffer saturation mechanism, progressive depletion (saturation) of free buffer by Ca2+ arriving with each new afferent action potential causes simultaneous increase in local Ca2+ transients, leading to short-term facilitation of synaptic response.

Facilitation by buffer saturation can be described as a non-linear summation of free Ca2+ elevations produced by the opening of Ca2+ channels arriving at the same active zone at different points in time. In this work we use computational modeling to examine the potential impact of buffer saturation on non-local interaction of Ca2+ fluxes arriving through spatially separated groups of channels. In this case a Ca2+ influx at a single active zone or a group of co-localized active zones would deplete (saturate) Ca2+ buffers throughout an axonal segment, leading to an amplification of Ca2+ influx arriving at a remote active zone. Note that such non-linear summation of Ca2+ fluxes arriving through spatially distant sources is achieved without a concomitant increase in free Ca2+, provided that the affinity of the buffer is sufficiently high. Such "non-local" interaction of Ca2+ signals necessarily requires highly mobile buffers. Like in the case of local buffer saturation, it also requires buffers of optimal concentration. We examine the dependence of this effect on the geometric parameters and the calcium-binding properties of the Ca2+ buffer.

Ralph Nossal (National Institutes of Health) 4:15-4:40

Probabilistic Aspects of Clathrin-Mediated Synaptic Membrane Activity

Abstract: Clathrin-mediated endocytosis (CME) plays an important role in the overall regulation of chemically mediated neural communication. After synaptic vesicles fuse with regions of plasma membrane, excess membrane that has been delivered to pre-synaptic nerve terminals is recycled. Correspondingly, in postsynaptic target cells, surface-expressed molecules such as NMDA receptors are directed away from the membrane into specific endocytic pathways. CME is central to these and other associated trafficking events. Studies of tissue culture models of receptor-mediated endocytosis, such as those involving the transferring receptor, indicate that productive clathrin-coated pits (those which result in coated vesicles) arise via stochastic processes. We recently derived analytical equations that link the fate probabilities of coated pits to various system parameters, including the elasticity coefficients of vesicle membranes and protein coats, stabilizing energies of coat formation, cellular concentrations of pit components, and energies associated with the binding of endocytic cargo. These results are discussed in relation to several aspects of synaptic activity.

Closing Remarks 4:45